REMARKS

Claims 1-83 are pending in the current application. Applicants provisionally elected claims 1-16, 22-24, 32-33, 36-38, 43, 80, 82 and 83 in response to the Restriction Requirement issued by the Examiner on October 2, 2002 (Paper No. 6). In the Office Action issued on June 26, 2003 (Paper No. 9), the Examiner further withdrew claims 22-24, 80, 82 and 83 as being drawn to a non-elected invention. Claims 1-16, 32, 33, 36-38 and 43 are therefore under examination. By way of the present Amendment, Applicants amend claims 1-4, 12, 13 and 15 and request consideration of claims 22-24, 80, 82 and 83.

Information Disclosure Statement

Applicants acknowledge the Examiner's observation that an Information Disclosure Statement (IDS) had not been entered into the instant application as of the time of the preparation of the Office Action mailed on June 26, 2003 (Paper No. 9). Applicants hereby note that an IDS, with accompanying fee, is being properly submitted herewith, and respectfully request consideration of said IDS.

Objections to the Specification

The Examiner has objected to the title of the instant invention as not being sufficiently descriptive. Applicants have amended the title herein to "Novel Fibroblast Growth Factor (FGF23) Nucleic Acids," as set forth in greater detail above.

The Examiner also objected to the specification as improperly containing embedded hyperlinks. As set forth in greater detail above, Applicants have amended the specification herein to delete all embedded hyperlinks and browser-executable code.

The Examiner also objected to the specification for citing an amino acid sequence of "4 or more" amino acids without using a SEQ ID NO: for reference to such amino acid sequence. As set forth in greater detail above, Applicants have amended the specification herein to properly identify all sequences of four or more amino acids with a SEQ ID NO:. Specifically, Applicants have amended the paragraph beginning at line 11 of page 10 and ending at line 12 of page 10 to now recite "...where the predicted signal

peptide and RXXR/S (SEQ ID NO:35) protease cleavage sites are indicated."

Accordingly, Applicants respectfully submit that all of the Examiner's objections to the specification have been overcome and respectfully request withdrawal of the objections. No new matter has been added by the way of the amendments made to the present application in order to overcome the Examiner's objection to the specification.

Objections to the Claims

The Examiner objected to claims 1-16, 32-33, 36-38 and 43 because, in the Examiner's view, the claims, as written, contain reference to non-elected inventions. In view of Applicants' election of SEQ ID NO:1 for prosecution, Applicants have amended claims 2 and 13 to delete reference to SEQ ID NO:3. Applicants have also amended claim 3 to delete reference to SEQ ID NO:4. Accordingly, Applicants respectfully submit that the Examiner's objection to the claims has been overcome.

Restriction Requirement/Claim Election

On March 31, 2003, in response to the Examiner's Restriction Requirement mailed on October 2, 2002 (Paper No. 6), Applicants elected to prosecute Group I claims, claims 1-16, 22-24, 32-33, 36-38, 43, 80, 82 and 83, and provisionally elected to prosecute SEQ ID NO:1 as set forth in the as-filed application.

In the present Office Action, the Examiner has further withdrawn claims 22-24, 80, 82 and 83 as being drawn to the non-elected invention. Apparently, it is the Examiner's view that claims 22-24, 80, 82 and 83 are drawn to mutants of FGF23 that are not encompassed by the elected invention. Applicants respectfully disagree with the Examiner for the following reasons.

As set forth in detail below in response to the Examiner's written description and enablement rejections, Applicants respectfully submit that the instant application properly encompasses wild type as well as mutant FGF23 polypeptides encoded by wild type and mutant FGF23 polynucleotides, respectively. Specifically, as the claims have been amended herein, the instant invention encompasses polynucleotides comprising SEQ ID NO:1 and encoding polypeptides having the biological activity of

FGF23, polynucleotides having at least 99% identity to SEQ ID NO:1 and encoding polypeptides having the biological activity of FGF23, and polynucleotides encoding polypeptides having at least 98% identity to SEQ ID NO:2 and having the biological activity of FGF23. Therefore, the present invention encompasses a genus of FGF23 molecules comprised of wild type FGF23, as well as a finite number of mutants of FGF23, based on sequence homology with the wild type FGF23, wherein such mutants further necessarily possess the biological activity of FGF23. One of skill in the art would therefore understand Applicants' instant invention to encompass mutants of FGF23 polynucleotides, as Applicants have provided extensive support for a representative number of such mutants of FGF23 set forth in SEQ ID NO:1.

Applicants respectfully remind the Examiner that there are two criteria that must be met for restriction of what the Examiner believes to be "patentably distinct" inventions. (See MPEP 803). First, the inventions must be independent or distinct as claimed. Further, there must be a serious burden on the Examiner if restriction is required. The Examiner has not set forth any reasoning as to why a search of more than one sequence of the present invention would pose an undue burden.

Applicants respectfully contend that by searching SEQ ID NO:1 as set forth in the claims elected in Applicants' response to the Restriction Requirement, the Examiner will identify not only the exact sequence as set forth in SEQ ID NO:1, but also, any homolog of SEQ ID NO:1, including the polynucleotides set forth in the elected claims. Accordingly, Applicants respectfully submit that the search will not impose an undue burden on the Examiner.

Further, Applicants point out to the Examiner that the present application contains numerous examples of sequences homologous to the FGF23 sequence set forth in SEQ ID NO:1 of the application, which sequences would be understood by one of skill in the art to be identified in a search of SEQ ID NO:1. According to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, 'Written Description' Requirement" (Federal Register, Vol. 66, No. 4, Friday, January 5, 2001, pp. 1099-1111), the written description requirement for a genus may be satisfied by the actual reduction to practice of a representative number of species:

> For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a),above), reduction to drawings (see (1)(b), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... (emphasis added) (Federal Register, Vol. 66, No. 4, Friday, January 5, 2001, p 1106).

Applicants' specification satisfies the above-listed written description requirements, and therefore, Applicants' invention properly includes the entire genus as claimed in the amended claims presented herein. As described in greater detail below, Applicants have described in the instant specification the sequence, structure, and functional properties of wild type FGF23, encoded by the polynucleotide set forth in SEQ ID NO:1. Applicants have also described the sequence, structure, and functional properties of several FGF23 mutants having polypeptide sequences at least 98% identical to wild type FGF23 as set forth in SEQ ID NO:2 and being encoded by polynucleotide sequences at least 99% identical to wild type FGF23 as set forth in SEQ ID NO:1. Examples of such FGF23 mutants found in the specification include, but are not limited to, R176Q FGF23, R179Q FGF23, and R179W FGF23. Applicants submit that one of skill in the art, based on the disclosure provided in the instant specification, would know how to make and use FGF23 mutants as claimed in the amended claims presented herein.

Applicants respectfully submit that, based on the extensive support in the specification, the elected invention properly encompasses mutants of FGF23 as claimed in the amended claims presented herein, and that Applicants are properly entitled to such scope in the claims. Further, for the reasons presented and supported in this Response to Office Action, Applicants submit that the entire genus of FGF23 polynucleotides and polypeptides of the instant invention is represented by a sufficient description of a representative number of species by actual reduction to practice and by functional characteristics coupled with a known disclosed correlation between function and structure. Therefore, Applicants respectfully submit that the Restriction Requirement imposed by the Examiner may no longer apply in light of Applicants' arguments set forth

herein.

Applicants further respectfully submit that, if the Examiner maintains the requirement of the sequence election, the Examiner's position with respect to the sequence election does not negate Applicants' right to obtain allowance of claims that are not restricted solely to SEQ ID NO:1.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has set forth several rejections under 35 U.S.C. § 112, second paragraph. First, it is the Examiner's view that claim 1 is indefinite for recitation for recitation of the term "fibroblast growth factor-23" without further characterization of the fibroblast growth factor-23 being claimed. Applicants have amended claim 1 to recite "...fibroblast growth factor-23 (FGF23) as set forth in SEQ ID NO:1..." Accordingly, Applicants respectfully submit that claim 1 distinctly claims the subject matter of the invention, and therefore, the Examiner's rejection has been overcome.

Secondly, the Examiner has rejected claims 2 and 3 as being indefinite for recitation of the articles "a" and "an" in reference to the SEQ ID NOs in the claims. Applicants have amended claims 2 and 3 to recite, for example, "the nucleic acid sequence of SEQ ID NO:1." Accordingly, Applicants respectfully submit that claims 2 and 3 distinctly claim the subject matter of the invention, and therefore, the Examiner's rejections of claims 2 and 3 have been overcome.

The Examiner has also rejected claim 2 as being indefinite for recitation of the phrase "at least about 50%," because in the Examiner's view, the term "about" does not provide a lower limit of percent identity. Applicants submit that the amendments made to claim 2 in response to the written description rejection, as set forth in detail below, render the Examiner's indefiniteness rejection of claim 2 moot, as the alleged offending language has been removed from the claim.

The Examiner has rejected claim 4 as indefinite for recitation of the term "included" in reference to the deposit number in the claim. Applicants have amended claim 4 herein to read "An isolated FGF23 nucleic acid included in DMSZ Deposit No. DSM 13530..." Applicants respectfully submit that the insertion of the term "FGF23" indicates that a particular DNA is included in the deposit, and therefore, claim 4, as

amended, particularly directs one of skill in the art how to obtain FGF23 from the deposited microorganism. Accordingly, Applicants respectfully submit that the Examiner's rejection of claim 4 has been overcome.

The Examiner has also rejected claims 7 and 15 as indefinite because, in the Examiner's view, the use of the term "specifying" is not clear. Applicants have amend claims 7 and 15 herein to delete the phrase "a nucleic acid specifying." For example, claim 7 now reads "...said nucleic acid further comprising a promoter/regulatory sequence operably linked thereto." Applicants respectfully submit that the Examiner's rejections of claims 7 and 15 have been overcome.

The Examiner has rejected claims 12 and 43 as indefinite for recitation of the phrase "being in an antisense orientation" and the term "complementary" in the same claim. In the Examiner's view, the claims are therefore redundant. Applicants respectfully point out that claim 43 does not recite the alleged offending language, and therefore, Applicants respectfully request clarification of the Examiner's rejection as it pertains to claim 43. Regarding claim 12, Applicants have amended claim 12 herein to delete the phrase "said complementary nucleic acid being in an antisense orientation." Accordingly, claim 12 no longer recites the alleged offending language, and Applicants respectfully submit that the Examiner's rejection has been overcome.

The Examiner has also rejected claim 43 as indefinite for recitation of the "biological activity of FGF23." It is the Examiner's view that the claim must include a recitation of the biological activity of FGF23. Applicants respectfully point out to the Examiner that the biological activity of FGF23 is explicitly defined from line 27 through line 32 on page 20 of the specification, and therefore need not be included in the claim.

Specifically, Applicants defined the biological activity of FGF23 as "the ability of a molecule to bind to an FGF receptor and alter phosphate transport in vivo or in vitro." Additionally, Applicants submit that the entire specification describes the role of FGF23 in phosphate homeostasis. For example, Example 1 beginning on page 54 of the specification describes the role of FGF23 in Autosomal Dominant Hypophosphatemic Rickets (ADHR), a disorder of phosphate homeostasis. Therefore, one of skill in the art would understand, based on the disclosure of the instant specification, that an FGF23 molecule of the instant invention has biological activity which includes the ability to

regulate phosphate homeostasis. Further, because claim 43 ultimately claims the sequence set forth in claim 1 – SEQ ID NO:1 – Applicants respectfully submit that claim 43 indeed specifically points out and distinctly claims the subject matter of the invention, namely, a molecule with the sequence of FGF23 as set forth in SEQ ID NO:1 or SEQ ID NO:2, and the biological activity including the ability to regulate phosphate homeostasis. Accordingly, Applicants respectfully contend that the Examiner's rejection of claim 43 for indefiniteness based on the definition of the biological activity of FGF23 is improper and should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph – written description

The Examiner has rejected claims 1-3, 5-16, 36-38 and 43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time of filing. Specifically, it is the Examiner's view that Applicants do not have sufficient written description for any "mutant, variant, fragment or homolog" of the FGF23 polypeptide other than the specific FGF23 mutants disclosed in the specification and containing mutations at position 176 or 179. Similarly, it is the Examiner's view that Applicants do not have sufficient written description for any "mutant, variant, fragment or homolog" of the FGF23 polynucleotide other than those FGF23 polynucleotides that encode FGF23 polypeptides containing mutations at position 176 or 179 as disclosed in the specification.

While not necessarily agreeing with the Examiner's reasoning, but in a good faith effort to expedite prosecution in the instant application, Applicants have amended independent claims 1-3 and 12 to delete language directed to non-specific fragments, variants and homologs of FGF23. Additionally, as described above in response to the Examiner's rejections pursuant to 35 U.S.C. § 112, second paragraph, Applicants have amended claim 1 to recite "...FGF23 comprising SEQ ID NO:1..." Further, Applicants have amended claim 2 such that claim 2 is now drawn to a nucleic acid with at least 99% identity to the FGF23 sequence set forth in SEQ ID NO:1. Similarly, claim 3 has been amended such that claim 3 is now drawn to a nucleic acid encoding a polypeptide with at least 98% identity to the FGF23 sequence set forth in

SEQ ID NO:2.

Applicants respectfully submit that claims 1-3 and 12, and consequently, dependent claims 5-11, 13-16, 36-38 and 43, are in full compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. Regarding written description support for FGF23 polynucleotides of the instant invention, Applicants direct the Examiner's attention to the passage beginning at line 24 of page 12 and extending through line 4 on page 13 of the specification, which passage provides explicit support for polynucleotides having at least 99% identity to the FGF23 polynucleotide set forth in SEQ ID NO:1.

Further, Figures 10A and 10B describe in detail specific mutations of arginine residues at either or both of amino acid positions 176 and 179, with respect to the FGF23 sequence set forth in SEQ ID NO:2. Preparation of an FGF23 polynucleotide encoding FGF23 polypeptides having mutations of the arginines at positions 176 or 179 of SEQ ID NO:2 to glutamines, as taught in extensive detail in Example 3 in the instant specification, would be understood by one of ordinary skill in the art as more than an adequate written description of the instant invention. Further still, Applicants' reduction to practice of the above-described FGF23 mutants of the instant invention indisputably demonstrates "possession" of polynucleotides (as well as polypeptides) of the presently-claimed invention, as required by the written description requirements of 35 U.S.C. § 112, first paragraph.

Regarding written description support for FGF23 polypeptides of the instant invention, Applicants direct the Examiner's attention to the passage at lines 18-29 on page 24 of the specification, which passage provides explicit support for polypeptides having at least 98% identity to the FGF23 polypeptide set forth in SEQ ID NO:2. Specifically, Applicants describe the polypeptide sequence of FGF23 and FGF23 mutant polypeptides, as well as the biological activity of FGF23 and FGF23 mutant polypeptides. For example, Applicants describe that R176Q, R179W, and R179Q mutants of the FGF23 polypeptide set forth in SEQ ID NO:2 have been shown to have increased stability, and therefore, demonstrate the "biological activity" of FGF23 for a period of time longer than the biological activity observed in the presence of wild type FGF23 polypeptide. One biological activity of such mutant FGF23 polypeptides is the

ability to effect Autosomal Dominant Hypophosphatemic Rickets (ADHR), the physiological symptoms of which are well known in the art.

Applicants have also amended claims 1-4 to include functional language directed to the "biological activity of FGF23." As described above in response to the Examiner's rejections pursuant to 35 U.S.C. § 112, second paragraph, the biological activity of FGF23 is explicitly defined from line 27 through line 32 on page 20 of the instant specification, and therefore need not be included in the claim. Therefore, in addition to describing the invention by way of the polynucleotide and polypeptide sequences set forth in SEQ ID NOS:1 and 2, and by way of several representative examples of mutants of SEQ ID NOS:1 and 2, Applicants have also particularly described biological activity of the wild type and mutant FGF23 molecules of the instant invention. Applicants respectfully submit that functional language in the claims will be understood by one of skill in the art to demonstrate Applicants' possession of the present invention at the time of filing, as such functional language, taken in conjunction with the sequence of FGF23 of the claimed invention, is evidence of sufficient identifying characteristics of the present invention. Accordingly, Applicants respectfully submit that the claims, as amended, satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph – enablement

The Examiner has rejected claims 1-16, 32, 33, 36-38 and 43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. In the Examiner's view, the specification is enabling for the isolated nucleic acid molecule of SEQ ID NO:1, but not for "mutants, variants, homologs, and fragments" of SEQ ID NO:1, nucleic acids having about 50% sequence identity to SEQ ID NO:1, or nucleic acids encoding proteins having about 40% identity to the protein encoded by SEQ ID NO:1.

Applicants respectfully submit that the above-described amendments to the claims made herein in response to the written description rejection also serve to overcome the Examiner's rejection for lack of enablement. In particular, Applicants

direct the Examiner's attention to claim 1, and therein to the specific recitation of "SEQ ID NO:1," and submit that amended claim 1 is drawn to an isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) as set forth in SEQ ID NO:1, wherein the polypeptide encoded by said nucleic acid has the biological activity of FGF23. Applicants also direct the Examiner's attention to amended claims 2 and 3, which are now drawn to "an isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) wherein said isolated nucleic acid shares at least 99% sequence identity with the nucleic acid sequence of SEQ ID NO:1, and wherein the polypeptide encoded by said nucleic acid has the biological activity of FGF23," and "an isolated nucleic acid encoding a fibroblast growth factor-23 (FGF23) wherein said isolated nucleic acid encodes a polypeptide having an amino acid sequence that shares at least 98% sequence identity with the amino acid sequence of SEQ ID NO:2, wherein said polypeptide has the biological activity of FGF23," respectively. The above-described amendments are supported throughout the specification as filed, which discloses the sequences of wild type FGF23 and mutant FGF23 molecules, such that these amendments add no new matter.

Applicants respectfully submit that claims 1-16, 32, 33, 36-38 and 43 do not recite "any" fragments, variants, or homologs of FGF23, and therefore, do not require undue experimentation. Rather, the claims – and in particular, claims 2 and 3 – are drawn to wild type FGF23, and to a finite number of well-defined FGF23 homologs. The claims, as amended, are drawn to FGF23 homologs having at least 99% identity to wild type FGF23, which homologs necessarily have the biological activity of wild type FGF23. As described in greater detail above in response to the written description rejection, lines 18-29 on page 24 of the specification provides explicit support for polypeptides having at least 98% identity to the FGF23 polypeptide set forth in SEQ ID NO:2. Specifically, Applicants describe therein the polypeptide sequence of FGF23 and FGF23 mutant polypeptides, as well as the biological activity of FGF23 and FGF23 mutant polypeptides. For example, Applicants describe that a R176Q mutant of the FGF23 polypeptide set forth in SEQ ID NO:2 has been shown to have increased stability, and therefore, demonstrate the "biological activity" of FGF23 for a period of time longer than the biological activity observed in the presence of wild type FGF23 polypeptide.

Again, these amendments are supported throughout the specification as filed, which discloses wild type and mutant sequences of SEQ ID NOS:1 and 2 and provides numerous working examples of the present invention. For example, Examples 1, 2, 3, 4, and 5 of the instant application describe in detail how one of ordinary skill in the art would identify and isolate wild type and mutant FGF23, assay the biological activity of wild type and mutant FGF23, and characterize the properties of wild type and mutant FGF23. Applicants respectfully submit that the above-detailed working examples are presented with abundant guidance such that it would not require more than ordinary and routine experimentation for skilled artisan to practice the instant invention.

In sum, the Examiner's rejections of claims 1-16, 32, 33, 36-38 and 43, pursuant to 35 U.S.C. § 112, first paragraph, for lack of enablement have been overcome or rendered moot and should be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 12 were rejected under 35 U.S.C. § 102(b) as being anticipated by Mahmood et al. (1995, Develop. 121:1399-1410). Specifically, it is the Examiner's view that Mahmood et al. discloses a polynucleotide which comprises at least a single nucleotide in common with SEQ ID NO:1.

In order for a rejection under 35 U.S.C. § 102(b) to be proper, each and every element of the invention must be disclosed by the cited reference. However, the Mahmood reference does not teach each and every element of the instant claimed invention. As claims 1 and 12 have been amended herein, described above in greater detail, Applicants' claimed invention includes polynucleotides at least 99% identical to SEQ ID NO:1. Mahmood does not teach a polynucleotide encompassed by Applicants instant claimed invention, and therefore, Mahmood does not anticipate the instant invention. Accordingly, applicants respectfully request withdrawal of the rejection.

Summary

The amendments made herein are supported in the as-filed specification, and as such, no new matter has been added by way of the present amendment. Applicants respectfully submit that each and every rejection or objection set forth by the

Examiner has either been overcome or is now inapplicable, and that the instant application is in full condition for allowance. Favorable examination of the claims on the merits is respectfully requested.

Respectfully submitted,

MICHAEL ECONS *ET AL.*

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(Date)

By: _____

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